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SCHEDULE 3

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PHARMACOKINETICS

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3. Doherty, J. E., Perkins, W. H., and Flanigan, W. J.: The distribution and concentration of tritiated digoxin in human tissues, Ann. Int. Med., 66: 116 (1967).

4. Gibaldi, M., Levy, G., and Hayton, W.: Kinetics of the elimination and neuromuscular blocking effect of d-tubocurarine in man, Anesthesiol., 36: 213 (1972).

5. Kaplan, S. A., Jack, M. L., Alexander, K., and Weinfeld, R. E.: Pharmacokinetic profile of diazepam in man following single intravenous and oral and chronic oral administrations, J. Pharm. Sci., 62: 1789 (1973).

6. Nagashima, R., Levy, G., and O'Reilly, R. A.: Comparative pharmacokinetics of coumarin anticoagulants. IV. Application of a three-compartment model to the analysis of the dose-dependent kinetics of bishydroxycoumarin elimination, J. Pharm. Sci., 57: 1888 (1968).

Chapter 3

MULTIPLE DOSING

Some drugs, e.g., analgesics, hypnotics, neuromuscular blocking agents, bronchodilators, and antiemetics, may be used effectively as a single dose. More frequently, drugs are given on a continuous basis. Moreover, most drugs are administered with sufficient frequency that measureable and, often, pharmacologically significant, levels of drug persist in the body when a subsequent dose is administered. For drugs administered in a fixed dose at a constant dosing interval, e.g., every 6 hr or once a day, the peak plasma level following the second and succeeding doses of a drug is higher than the peak level after the first dose, and therefore the drug accumulates in the body relative to the initial dose. However, under these conditions drug accumulation proceeds at a decreasing rate with increasing number of doses until a steady-state plasma level of drug is achieved. At steady state, the plasma concentration of drug at any point in time during any dosing interval will be identical. As will be demonstrated, the rate and extent of accumulation of a drug is a function of the relative magnitudes of the dosing interval and the half-life of the drug. A model-independent approach to multiple dosing is discussed in Appendix 5.

I. ONE-COMPARTMENT MODEL

A. Intravenous Injection

Following the intravenous injection of a drug, the maximum amount of drug in the body $(X_1)_{max}$ would equal the dose X_0, that is,

$$(X_1)_{max} = X_0 \tag{341}$$

As illustrated in Chap. 1, the amount of drug in the body X as a function of time t for a drug that confers one-compartment characteristics to the body following rapid intravenous injection may be described by

$$X = X_0 e^{-Kt} \tag{5}$$

where K is the apparent first-order elimination rate constant of the drug and is related to the half-life of the drug ($t_{\frac{1}{2}} = 0.693/K$). Therefore, the amount of drug in the body at the end of a dosing interval of length τ time units will be given by the relationship

$$X = X_0 e^{-K\tau} \tag{342}$$

Since the amount of drug in the body at the end of a dosing interval (i.e., immediately prior to the administration of a second dose) is a minimum (Fig. 3-1), Eq. (342) may be written as

$$(X_1)_{min} = X_0 e^{-K\tau} \tag{343}$$

where $(X_1)_{min}$ is the minimum amount of drug in the body after the first dose.

Administration of a second dose, equal in size to the first dose, would produce an immediate increase in the body levels of drug yielding a new maximum $(X_2)_{max}$ which would be equal to the sum of the amount of drug in the body at the time of administration (i.e., at time $t = \tau$) and the administered dose. Therefore,

$$(X_2)_{max} = X_0 + (X_1)_{min} = X_0(1 + e^{-K\tau}) \tag{344}$$

where $(X_1)_{min}$ is given by (343). The minimum amount of drug in the body after the second dose $(X_2)_{min}$ (assuming a constant dosing interval of τ) is given by

$$(X_2)_{min} = (X_2)_{max} e^{-K\tau} = X_0(1 + e^{-K\tau})e^{-K\tau} \tag{345}$$

which can be modified to yield

$$(X_2)_{min} = X_0(e^{-K\tau} + e^{-2K\tau}) \tag{346}$$

It follows that

$$(X_3)_{max} = X_0 + X_0(e^{-K\tau} + e^{-2K\tau}) = X_0(1 + e^{-K\tau} + e^{-2K\tau}) \tag{347}$$

and

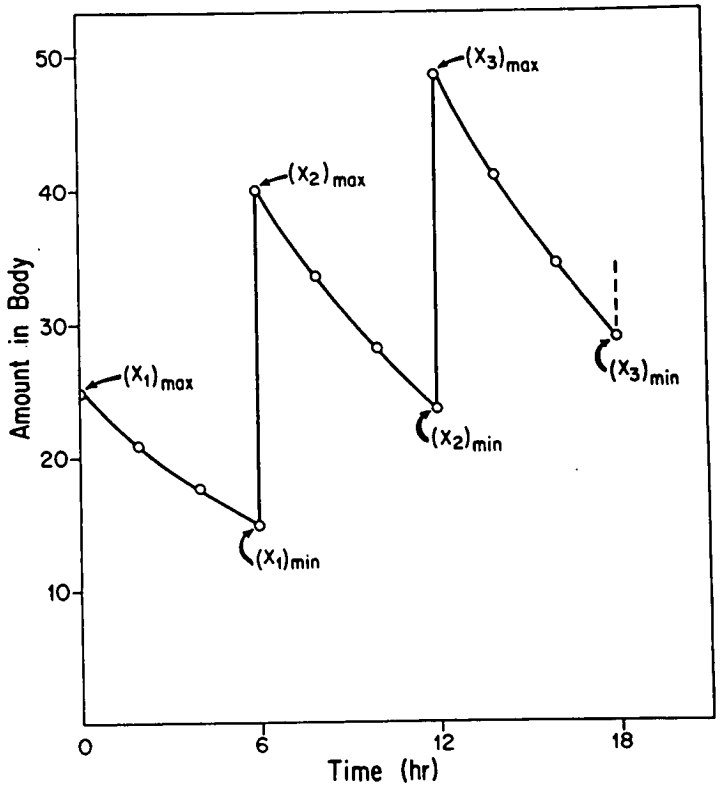

FIG. 3-1. A plot of the amount of drug in the body as a function of time following the intravenous administration (at equal time intervals) of three equal doses of a drug that confers one-compartment model characteristics on the body.

$$(X_3)_{min} = X_0(1 + e^{-K\tau} + e^{-2K\tau})e^{-K\tau} = X_0(e^{-K\tau} + e^{-2K\tau} + e^{-3K\tau}) \tag{348}$$

where $(X_3)_{max}$ is the maximum amount of drug in the body following a third dose and $(X_3)_{min}$ is the minimum amount of drug in the body τ time units after the third dose.

On examination of (341), (344), and (347) it is readily apparent that a geometric series can be written for the maximum amount of drug in the body following n doses, $(X_n)_{max}$, that is

$$(X_n)_{max} = X_i(1 + e^{-K\tau} + e^{-2K\tau} + \cdots + e^{-(n-1)K\tau}) \tag{349}$$

If we let

$$r = 1 + e^{-K\tau} + e^{-2K\tau} + \cdots + e^{-(n-1)K\tau} \tag{350}$$

it follows that

$$(X_n)_{max} = X_0 r \tag{351}$$

Multiplication of (350) by $e^{-K\tau}$ yields

$$re^{-K\tau} = e^{-K\tau} + e^{-2K\tau} + \cdots + e^{-(n-1)K\tau} + e^{-nK\tau} \tag{352}$$

which when subtracted from (350) produces

$$r - re^{-K\tau} = 1 - e^{-nK\tau} \tag{353}$$

which can be solved for r to yield

$$r = \frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}} \tag{354}$$

Substitution of this value of r in (351) yields the following general expression for the maximum amount of drug in the body after intravenous administration of any number of doses:

$$(X_n)_{max} = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right) \tag{355}$$

From a comparison of previous equations [that is, Eqs. (341) and (343), (344) and (345), and (347) and (348)] it is equally clear that

$$(X_n)_{min} = (X_n)_{max} e^{-K\tau} \tag{356}$$

and, therefore,

$$(X_n)_{min} = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-K\tau} \tag{357}$$

It is evident on examination of (355) and (357) that the amount of drug in the body at any time during a dosage interval (that is, X_n) is given by

$$X_n = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} \tag{358}$$

where t is the time elapsed since dose n was administered. Equation (358) may also be written in concentration terms since $X = V \cdot C$ [according to Eq. (9)], that is

$$C_n = \frac{X_0}{V}\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} \tag{359}$$

where C_n is the plasma concentration of drug during a dosing interval and V is the apparent volume of distribution of the drug. Therefore, by knowing the apparent volume of distribution and the elimination rate constant of a drug (both of which can be obtained following a single intravenous dose), the plasma concentration of a drug at any time during a dosing interval can be predicted provided a fixed dose is administered every τ time units.

Equations (358) and (359) may also be obtained by a method that does not rely on a detailed derivation of the type presented above, and consequently is significantly more convenient (see Appendix 2). Any equation which describes the time course of a drug in a driving force compartment after a single dose may be directly converted to a multiple-dose equation by multiplying each exponential term containing t by the function

$$\frac{1 - e^{-nk_i\tau}}{1 - e^{-k_i\tau}}$$

where n and τ are as defined previously and k_i is the apparent first-order rate constant in each exponential term. Therefore, multiplication of Eq. (5), $X = X_0 e^{-Kt}$, by the multiple-dosing function, and setting k_i equal to K [since K is the rate constant in the exponential term of (5)], Eq. (5) may be directly converted to (358), that is

$$X\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right) = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} = X_n$$

The drug concentration in the plasma, at any given point in time during a dosing interval, will increase as the number of doses increases and approach a constant level (see Fig. 3-2). After multiple dosing for a time equal to four times the biologic half-life of a drug, the plasma concentration is within 10% of its plateau or steady-state level. After

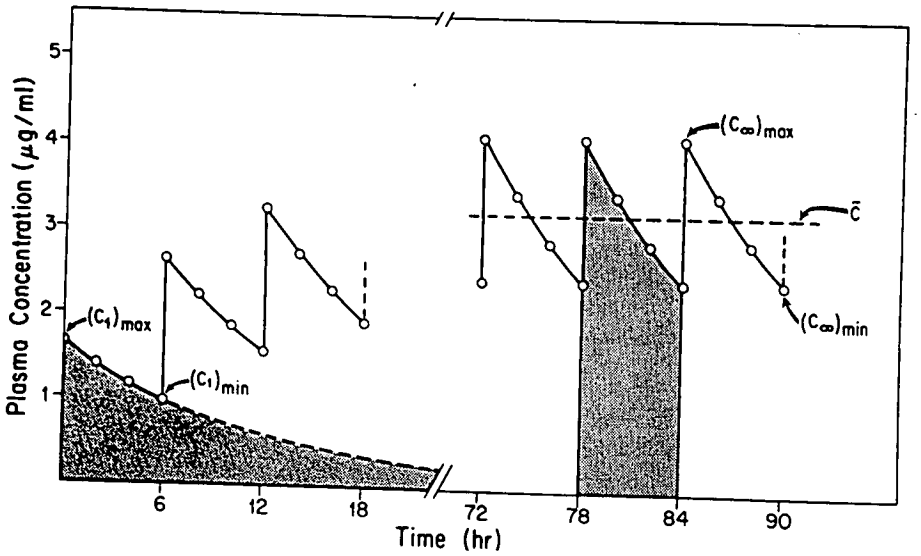

FIG. 3-2. A plot of plasma concentration versus time following the intravenous administration of equal doses of a drug, which confers one-compartment model characteristics on the body, at equal time intervals.

a period of time equal to 7 half-lives, the drug concentration, at any point in time during a dosing interval is within 1% of the plateau level. The equation describing the time course of drug at the plateau or steady-state level can be obtained by setting n in (359) to infinity (i.e., by recognizing that the term $e^{-nK\tau}$ approaches zero with increasing number of doses). Thus,

$$C_\infty = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-Kt} \tag{360}$$

where C_∞ is the plasma concentration of drug as a function of time during a dosing interval at steady state. Similarly the equations for the maximum and minimum amounts of drug in the body during a dosing interval at steady state, $(X_\infty)_{max}$ and $(X_\infty)_{min}$, respectively, can be written as

$$(X_\infty)_{max} = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) \tag{361}$$

and

$$(X_\infty)_{min} = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} \tag{362}$$

Equations (361) and (362) can also be expressed in concentration terms, employing the relationship $X = VC$ [Eq. (9)], as follows:

$$(C_\infty)_{max} = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) \tag{363}$$

and

$$(C_\infty)_{min} = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} \tag{364}$$

where $(C_\infty)_{max}$ and $(C_\infty)_{min}$ are the maximum and minimum plasma concentrations of drug at steady state, respectively.

A parameter which is very useful in multiple dosing is the "average" concentration of drug in the plasma at steady state, $\bar{C}$. This parameter can be defined as

$$\bar{C} = \frac{\int_0^\tau C_\infty \, dt}{\tau} \tag{365}$$

where $\int_0^\tau C_\infty dt$ is the area under the plasma concentration-time curve at steady state during a dosing interval, i.e., between time zero and τ, where τ is as defined previously. Integration of (360) from time zero to τ yields

$$\int_0^\tau C_\infty \, dt = \frac{X_0}{VK} \tag{366}$$

Substitution of X_0/VK for $\int_0^\tau C_\infty dt$ in (365) yields the following expression for $\bar{C}$:

$$\bar{C} = \frac{X_0}{VK\tau} \tag{367}$$

Therefore, by knowing the apparent volume of distribution and elimination rate constant of a drug, both of which can be determined following a single intravenous dose, the "average" plasma concentration of a drug at steady state following the intravenous administration of a fixed

dose X_0 at a constant time interval of τ can be predicted. As can also be seen from (367), only the size of the administered dose X_0 and the time interval at which this dose is administered, τ, can be adjusted to obtain a desired "average" steady-state plasma concentration since V and K are "biological" constants for a given drug.

The "average" plasma concentration of a drug at steady state as calculated employing (365) or (367) is neither the arithmetic nor the geometric mean of $(C_\infty)_{max}$ and $(C_\infty)_{min}$. Rather, it is the plasma concentration at steady state which when multiplied by τ equals the area under the plasma concentration-time curve over the time interval zero to τ. Therefore, from simple geometric considerations, $\bar{C}$ must represent some plasma concentration between $(C_\infty)_{max}$ and $(C_\infty)_{min}$ (see Fig. 3-2). A limitation of the $\bar{C}$ approach is that it gives no information about the fluctuations in plasma levels [that is, $\bar{C}$ gives no information as to the relative magnitudes of $(C_\infty)_{max}$ and $(C_\infty)_{min}$].

It should be noted that integration of Eq. (5), $X = X_0 e^{-Kt}$, which describes the time course of the amount of drug in the body following the administration of a single intravenous dose, from time zero to infinity gives

$$\int_0^\infty X\,dt = \frac{X_0}{K} \tag{368}$$

which when converted to concentration terms [that is, $X = VC$, Eq. (9)] yields

$$\int_0^\infty C\,dt = \frac{X_0}{VK} \tag{369}$$

This expression for the area under the plasma concentration-time curve from time zero to infinity following a single intravenous dose is equivalent to (366), the equation for the area under the plasma concentration-time curve from time zero to τ during a dosing interval at steady state. Hence, the area under the plasma concentration-time curve during a dosing interval at steady state is equivalent to the total area under the curve following a single dose (Fig. 3-2). Therefore, the "average" plasma concentration of drug at steady state can be predicted from a single-dose study by employing

$$\bar{C} = \frac{\int_0^\infty C\,dt}{\tau} \tag{370}$$

which does not require the calculation of the apparent volume of distribution and elimination rate constant. This equation does assume, however, that V and K are constant over the entire dosing period.

As discussed previously, the administration of a drug on a multiple-dose regimen will result in the accumulation of drug in the body. The extent of accumulation of a given drug may be quantified in several ways. During any dosing interval the "average" plasma concentration of a drug $\bar{C}_n$ may be defined as

$$\bar{C}_n = \frac{\int_0^\tau C_n\,dt}{\tau} \tag{371}$$

where $\int_0^\tau C_n\,dt$ is the area under the plasma concentration-time curve during the nth dosing interval. Integration of (359) from time zero to τ yields

$$\int_0^\tau C_n\,dt = \frac{X_0}{VK}(1 - e^{-nK\tau}) \tag{372}$$

and therefore,

$$\bar{C}_n = \frac{X_0}{VK\tau}(1 - e^{-nK\tau}) \tag{373}$$

Substitution of $\bar{C}$ for $X_0/VK\tau$, according to (367), in (373) and rearrangement yields

$$\frac{\bar{C}_n}{\bar{C}} = 1 - e^{-nK\tau} \tag{374}$$

When $n = 1$, that is, for the first dose, (374) becomes

$$\frac{\bar{C}_1}{\bar{C}} = 1 - e^{-K\tau} \tag{375}$$

The inverse ratio $\bar{C}/\bar{C}_1$ may be defined as an accumulation factor R, and therefore,

$$R = \frac{1}{1 - e^{-K\tau}} \tag{376}$$

By knowing the elimination rate constant, the extent to which a drug would accumulate in the body following a fixed dosing regimen can be calculated employing (376).

Other ratios may also be used to determine the extent of drug accumulation. Conversion of (343) and (341) to concentration terms [that is, using Eq. (9)] yields

$$(C_1)_{min} = \frac{X_0}{V} e^{-K\tau} \tag{377}$$

and

$$(C_1)_{max} = \frac{X_0}{V} \tag{378}$$

respectively. The ratios $(C_\infty)_{min}$ [Eq. (364)] to $(C_1)_{min}$ [Eq. (377)] and $(C_\infty)_{max}$ [Eq. (363)] to $(C_1)_{max}$ [Eq. (378)] all equal R, that is,

$$\frac{(C_\infty)_{min}}{(C_1)_{min}} = \frac{(C_\infty)_{max}}{(C_1)_{max}} = \frac{1}{1 - e^{-K\tau}} = R \tag{379}$$

Therefore, a comparison of minimum, maximum, and "average" plasma levels of drug following the first dose and at steady state enables one to gain insight into the extent to which a drug would be expected to accumulate on multiple dosing. Consider a drug with a half-life of 24 hr (that is, $K = 0.029\ hr^{-1}$, since $K = 0.693/t_{\frac{1}{2}}$). If this drug is administered every 24 hr (that is, $\tau = 24$ hr), R equals 2.0. However, administration every 6 hr results in greater than threefold increase in the extent of accumulation since R now equals 6.3.

Equation (367) can be rearranged to yield

$$\bar{C}V = \frac{X_0}{K\tau} \tag{380}$$

where $\bar{C}V$ equals the "average" amount of drug in the body at steady state ($\bar{X}$). Thus

$$\bar{X} = \frac{X_0}{K\tau} \tag{381}$$

Dividing both sides of (381) by X_0, the intravenous dose, substituting $0.693/t_{\frac{1}{2}}$ for K [according to Eq. (12)], and rearranging, results in the expression

$$\frac{\bar{X}}{X_0} = \frac{1.44t_{\frac{1}{2}}}{\tau} \tag{382}$$

which also enables an estimate of the extent of accumulation. When τ equals the half-life of a drug, the extent of accumulation is relatively modest. If the ratio $t_{\frac{1}{2}}/\tau$ is large, however, the extent of accumulation will become significant. For example, if τ is decreased from 24 to 6 hr for a drug with a 24-hr half-life, the "average" amount of drug in the body at steady state will be almost six times as large as a single dose.

Equation (374), in addition to its utility in determining the extent of accumulation, may also be employed to calculate the time required to reach a certain fraction of the ultimate steady-state level, where the fraction of the steady-state level, f_{ss}, is defined in terms of "average" plasma levels, that is,

$$f_{ss} = \frac{\bar{C}_n}{\bar{C}} \tag{383}$$

Substitution of f_{ss} for $\bar{C}_n/\bar{C}$ in (374) yields

$$f_{ss} = 1 - e^{-nK\tau} \tag{384}$$

Therefore, for a given half-life (that is, $t_{\frac{1}{2}} = 0.693/K$) and dosing interval the fraction of the ultimate steady-state level that is reached following the nth dose can be calculated. Rearrangement of (384) yields

$$e^{-nK\tau} = 1 - f_{ss} \tag{385}$$

the common logarithm of which is

$$-nK\tau = 2.303 \log (1 - f_{ss}) \tag{386}$$

Equation (386) can be further rearranged to obtain an expression for the time required to reach a certain fraction of the steady-state level, which is given by the product of the number of doses administered and the dosing interval. Thus,

$$n\tau = -\frac{2.303}{K} \log (1 - f_{ss}) \tag{387}$$

or

$$n\tau = -3.32t_{\frac{1}{2}} \log (1 - f_{ss}) \tag{388}$$

since K equals $0.693/t_{\frac{1}{2}}$ [Eq. (12)]. Therefore, the time required to reach a particular fraction of steady state (that is, $n\tau$) is independent of the number of doses administered and the interval between administration, but it is directly proportional to the half-life of a drug. From (388) it can be readily calculated that 3.32 and 6.64 half-lives would be required to reach 90 and 99%, respectively, of the steady-state plasma level of a drug.

As (388) indicates, a significant period of time may be required to attain steady-state plasma levels for drugs with long half-lives. A rational method to overcome the lapse in time before a steady-state level is reached would be to administer an initial "loading" dose. One approach to the calculation of a "loading" dose is as follows. It is often desirable to maintain plasma concentrations of drug greater than some minimum effective level. This level may be defined as $(C_\infty)_{min}$. Therefore, the first dose (i.e., the "loading" dose, X_0^*) must be sufficiently high such that $(C_1)_{min}$ equals $(C_\infty)_{min}$, where $(C_1)_{min}$ and $(C_\infty)_{min}$ are given by (377) and (364), respectively. Substitution of X_0^* for X_0 (the maintenance dose) in (377) yields

$$(C_1)_{min} = \frac{X_0^*}{V} e^{-K\tau} \tag{389}$$

Since $(C_1)_{min}$ as given by (389) must equal $(C_\infty)_{min}$,

$$\frac{X_0^*}{V} e^{-K\tau} = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} \tag{390}$$

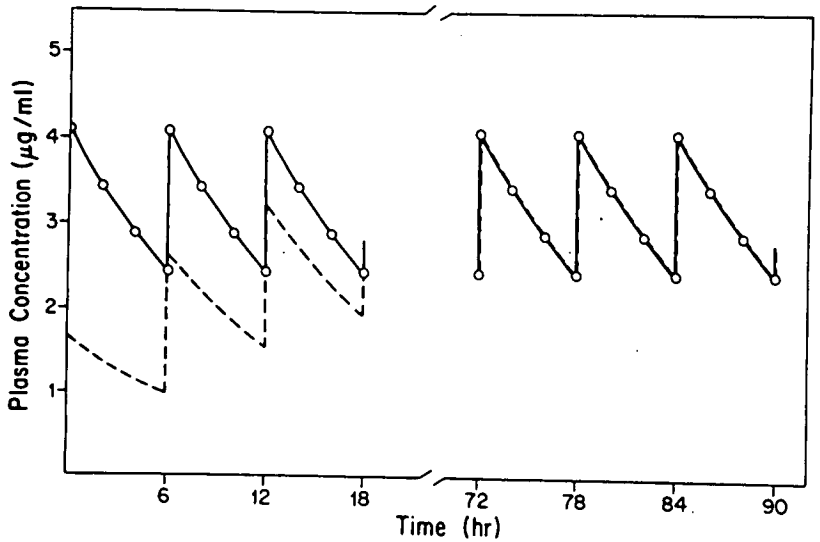

FIG. 3-3. A plot of plasma concentration versus time following repetitive intravenous administration of a drug which confers on the body the characteristics of a one-compartment model. The figure demonstrates the plasma levels resulting from the administration of either a series of maintenance doses (--) or an initial loading dose followed by a series of maintenance doses (o).

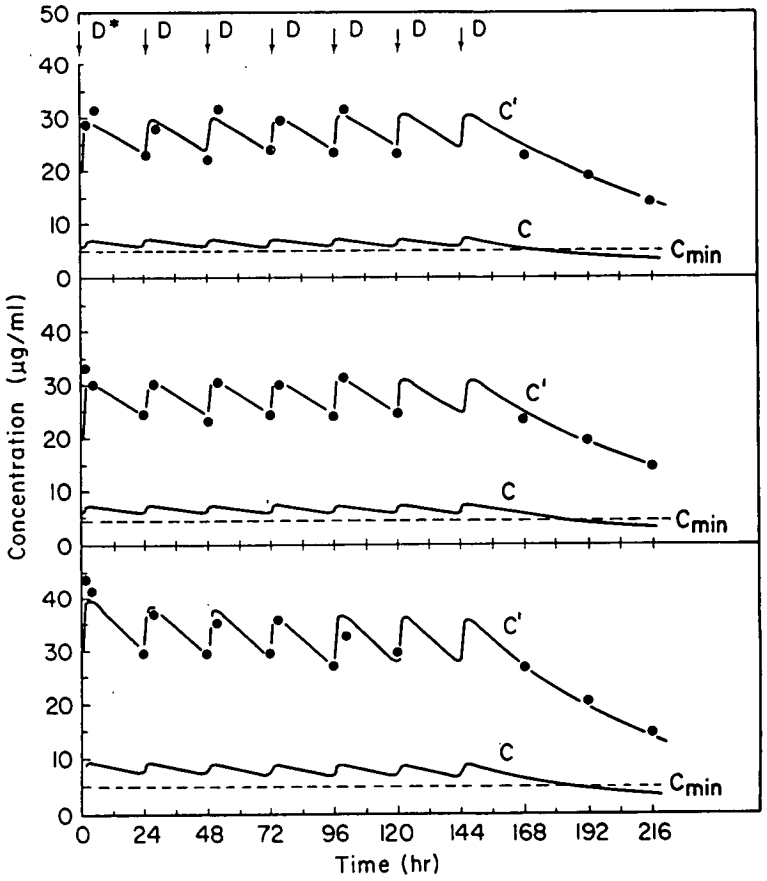

FIG. 3-4. Plasma concentrations (•) of 2-sulfa-3-methoxypyrazine in three normal adults during repetitive dosing. Loading dose $D^* = 400$ mg, maintenance dose $D = 100$ mg, $\tau = 24$ hr. Upper curves: c', calculated curves fitted to values found in plasma. Lower curves: c, calculated concentrations of unbound drug in plasma water. (From Ref. 1.)

By cancelling common terms the following expression for the determination of a "loading" dose is obtained:

$$X_0^* = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) \tag{391}$$

Therefore, administration of a "loading" dose X_0^* as calculated by (391) followed by a maintenance dose X_0 every τ time units, should produce an immediate steady-state plasma level of drug (Figs. 3-3 and 3-4).

The same procedure may be employed to calculate a "loading" dose based on the "average" plasma concentrations of drug. If this approach is used, an equation for the "loading" dose identical to (391) will be obtained. To illustrate this approach, let us consider a drug with a half-life of 24 hr which is administered every 24 hr. In this case, the "loading" dose X_0^* required to achieve immediate steady-state levels will be twice the size of the maintenance dose X_0.

B. First-order Absorption

The vast majority of drugs administered on a continuous basis are administered orally. Of these, a significant fraction yield plasma drug concentration-time curves which can be described by a one-compartment model with first-order input and output. The equation describing the plasma concentration versus time curve following multiple dosing of a drug which is absorbed by an apparent first-order process can be arrived at directly. Multiplication of each exponential term in Eq. (92), which describes the time course of drug in the plasma following first-order input, by the multiple-dosing function and setting k_i in each function equal to the rate constant in each exponential term (see Appendix 2) yields

$$C_n = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} - \left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t}\right] \qquad (392)$$

where C_n, V, K, n, and τ are as defined previously and t is any time from 0 to τ during a dosing interval. The constant k_a is the apparent first-order absorption rate constant and F is the fraction of the administered dose X_0 which is absorbed. Equation (392) can be employed to predict the plasma concentration of drug at any time during any dosing interval. However, information that is often difficult to obtain, such as estimates of F, V, and k_a, is required for such predictions.

At steady state the time course of drug in the plasma can be described by the equation

$$C_\infty = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-Kt} - \left(\frac{1}{1 - e^{-k_a\tau}}\right)e^{-k_a t}\right] \qquad (393)$$

which is obtained by setting n equal to a sufficiently large number in (392) and realizing that the terms $e^{-nK\tau}$ and $e^{-nk_a\tau}$ then approach zero.

The "average" plasma concentration of drug at steady-state $\bar{C}$, as defined by (365), can also be calculated either by employing (365) directly or by employing an equation analogous to (367) which can be derived as follows. Integration of (393) from time zero to τ yields

$$\int_0^\tau C_\infty \, dt = \frac{FX_0}{VK} \qquad (394)$$

where $\int_0^\tau C_\infty \, dt$ is the area under the plasma concentration-time curve during a dosing interval at steady state. Substitution of FX_0/VK for $\int_0^\tau C \, dt$ in (365) yields the following equation for the "average" plasma concentration of drug at steady state following first-order input:

$$\bar{C} = \frac{FX_0}{VK\tau} \qquad (395)$$

As is evident from (395), $\bar{C}$ is dependent on the size of dose administered, the extent to which it is absorbed, and the dosing interval. The same "average" plasma concentration of drug will be obtained whether or not the dose X_0 is administered as a single dose every τ time units, or is subdivided and administered at different times within τ time units; that is, 600 mg once a day is equivalent to 300 mg every 12 hr, is equivalent to 150 mg every 6 hr, etc. (see Figs. 3-5 and 3-6). However, upon subdividing the dose, the difference between the minimum and maximum plasma concentration will usually decrease.

The area under the plasma concentration-time curve from time zero to infinity ($\int_0^\infty C \, dt$) following first-order input of a single dose equals FX_0/VK [Eq. (98)], which is in turn equal to the area under the plasma concentration-time curve during a dosing interval at steady state [that is, $FX_0/VK = \int_0^\tau C_\infty \, dt$, Eq. (394)]. Therefore, substitution of $\int_0^\infty C \, dt$ for $\int_0^\tau C_\infty \, dt$ in (365) yields

$$\bar{C} = \frac{\int_0^\infty C \, dt}{\tau} \qquad (370)$$

This relationship is probably more useful than (395) for predicting $\bar{C}$ since the area under the plasma concentration-time curve following a single dose is generally easily determined. Estimates of F and V which are necessary for the utilization of (395) are frequently difficult to evaluate since intravenous data is usually required.

Assuming that the fraction F of each dose absorbed is constant during a multiple-dosing regimen, the time at which a maximum plasma concentration of drug at steady state occurs (t_p') may be arrived at by differentiating (393) with respect to time and setting the resultant equal to zero. Thus

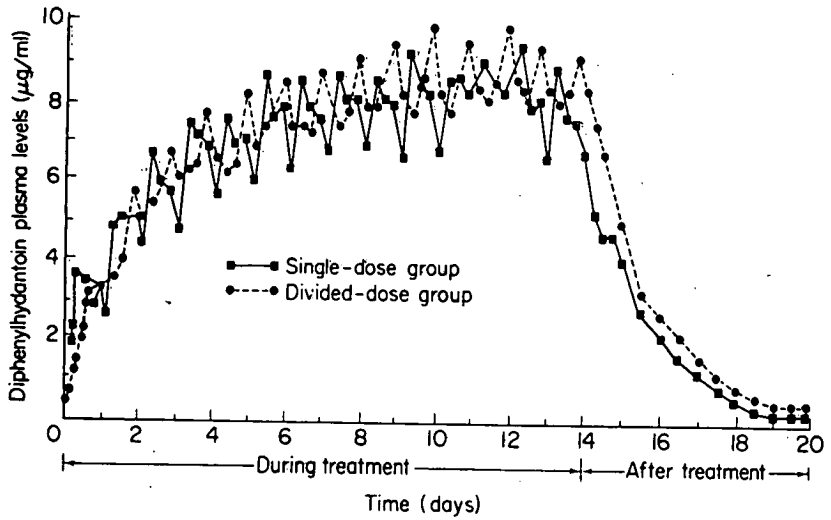

FIG. 3-5. Mean plasma levels of diphenylhydantoin (DPH) following oral administration of 100 mg DPH three times a day (divided-dose group) or 300 mg DPH once a day (single-dose group). Each group consisted of 12 normal adult volunteers. (From Ref. 2.)

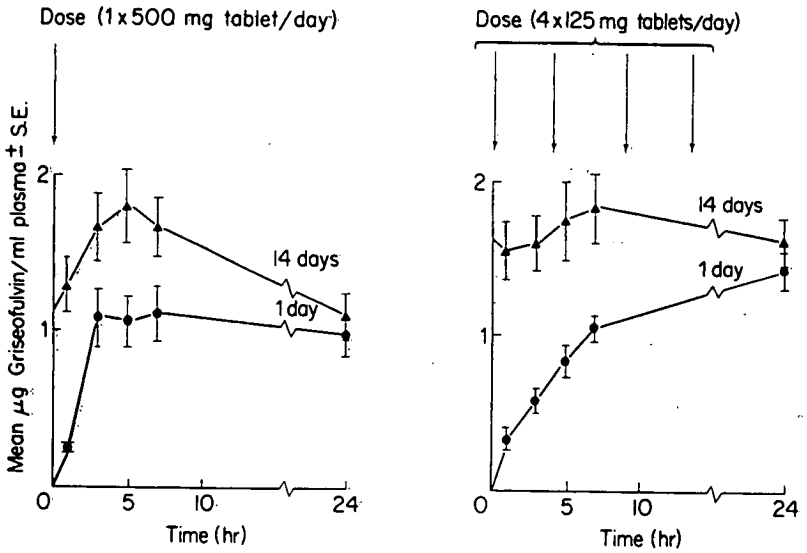

FIG. 3-6. Average plasma concentrations of griseofulvin in 10 human volunteers after 1 and 14 days of oral treatment. (From Ref. 3.)

$$\frac{dC_\infty}{dt} = \frac{k_a F X_0}{V(k_a - K)}\left(\frac{k_a e^{-k_a t'_p}}{1 - e^{-k_a \tau}} - \frac{K e^{-K t'_p}}{1 - e^{-K\tau}}\right) = 0 \tag{396}$$

and

$$\frac{k_a e^{-k_a t'_p}}{1 - e^{-k_a \tau}} = \frac{K e^{-K t'_p}}{1 - e^{-K\tau}} \tag{397}$$

Rearrangement of (397) yields

$$e^{(k_a - K)t'_p} = \frac{k_a(1 - e^{-K\tau})}{K(1 - e^{-k_a \tau})} \tag{398}$$

By taking the common logarithm of both sides of (398) and dividing by $k_a - K$, the following expression for the time at which the maximum plasma concentration at steady state occurs is obtained:

$$t'_p = 2.303 \log \frac{k_a(1 - e^{-K\tau})/K(1 - e^{-k_a \tau})}{k_a - K} \tag{399}$$

The time t_p at which a maximum plasma concentration occurs following a single dose is given by

$$t_p = 2.303 \log \frac{k_a/K}{k_a - K} \tag{104}$$

Subtraction of (399) from (104) yields

$$t_p - t'_p = 2.303 \log \frac{(1 - e^{-k_a \tau})/(1 - e^{-K\tau})}{k_a - K} \tag{400}$$

Since the right side of this equation is always positive, it is apparent that the maximum plasma concentration occurs at an earlier time at steady state than following a single dose. Frequently, the time at which the maximum plasma concentration is observed after the first dose t_p is the time at which the plasma is sampled after administration of subsequent doses. Based on mathematical principles this would not be a sound practice since the time at which a maximum plasma concentration

occurs is not constant until steady state is achieved. Moreover, biological variability would add to the undesirability of such an approach.

Once t_p' is known, the maximum plasma concentration at steady-state $(C_\infty)_{max}$ can be derived. Substitution of t_p' for time in (393) yields

$$(C_\infty)_{max} = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-Kt_p'} - \left(\frac{1}{1 - e^{-k_a\tau}}\right)e^{-k_a t_p'}\right] \quad (401)$$

By rearrangement of (397) the following expression for the term $e^{-k_a t_p'}$ can be obtained:

$$e^{-k_a t_p'} = \left(\frac{1 - e^{-k_a\tau}}{1 - e^{-K\tau}}\right)\frac{K}{k_a}e^{-Kt_p'} \quad (402)$$

Substituting this value of $e^{-k_a t_p'}$ into (401) yields

$$(C_\infty)_{max} = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-Kt_p'} - \left(\frac{1}{1 - e^{-k_a\tau}}\right)\left(\frac{1 - e^{-k_a\tau}}{1 - e^{-K\tau}}\right)\frac{K}{k_a}e^{-Kt_p'}\right] \quad (403)$$

which can be simplified to

$$(C_\infty)_{max} = \frac{FX_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-Kt_p'} \quad (404)$$

Following the first dose the maximum plasma concentration $(C_1)_{max}$ is given by

$$(C_1)_{max} = \frac{FX_0}{V}e^{-Kt_p} \quad (108)$$

Therefore, an accumulation factor R can be calculated since $R = (C_\infty)_{max}/(C_1)_{max}$ [Eq. (379)]. Thus,

$$R = \frac{1}{1 - e^{-K\tau}}\,\frac{e^{-Kt_p'}}{e^{-Kt_p}} \quad (405)$$

This is a relatively complicated relationship for the determination of accumulation since t_p and t_p' are complex functions of the absorption

and elimination rate constants, and consequently utilization of maximum plasma concentration values to quantify accumulation is not very attractive.

A simpler approach would be to compare the minimum plasma concentrations of drug at steady state and following the first dose to evaluate accumulation, that is, $R = (C_\infty)_{min}/(C_1)_{min}$ [Eq. (379)]. However, this method is relatively simple only when one is dealing with a situation in which each dose is administered in the postabsorptive phase of the preceding dose. This situation probably exists for a large number of the preceding dose. This situation probably exists for a large number of drugs although it may not be valid for sustained release products and for drugs which are very slowly absorbed.

By setting n equal to one and t equal to τ in (392), an expression for the minimum plasma concentration following the first dose $(C_1)_{min}$ can be obtained, that is,

$$(C_1)_{min} = \frac{k_a F X_0}{V(k_a - K)}(e^{-K\tau} - e^{-k_a\tau}) \quad (406)$$

Similarly, by setting t equal to τ in (393), the following expression for the minimum plasma concentration at steady state $(C_\infty)_{min}$ results:

$$(C_\infty)_{min} = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-K\tau} - \left(\frac{1}{1 - e^{-k_a\tau}}\right)e^{-k_a\tau}\right] \quad (407)$$

In the postabsorptive phase (that is, as $e^{-k_a\tau}$ approaches zero), (406) and (407) become

$$(C_1)_{min} = \frac{k_a F X_0}{V(k_a - K)}e^{-K\tau} \quad (408)$$

and

$$(C_\infty)_{min} = \frac{k_a F X_0}{V(k_a - K)}\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-K\tau} \quad (409)$$

respectively. Therefore, the accumulation factor $(C_\infty)_{min}/(C_1)_{min}$ is $R = 1/(1 - e^{-K\tau})$ [Eq. (376)]. This expression can be readily employed to determine the extent of accumulation following first-order input every τ time units since only an estimate of the elimination rate constant is required.

As discussed previously, following intravenous administration of a drug, the ratio $\bar{X}/X_0$ can also be used to estimate the extent to which

accumulation will occur following first-order input. Rearranging (395) and setting the product $\bar{C}V$ equal to $\bar{X}$, the average amount of drug in the body at steady state, yields

$$\bar{X} = \frac{FX_0}{K\tau} \tag{410}$$

Substitution of $0.693/t_{\frac{1}{2}}$ for K [Eq. (12)] and rearrangement gives

$$\frac{\bar{X}}{FX_0} = \frac{1.44t_{\frac{1}{2}}}{\tau} \tag{411}$$

where the extent of accumulation, as measured by comparing the "average" steady-state body level to the amount absorbed from the maintenance dose, is directly proportional to the ratio of the biologic half-life and dosing interval.

The time required to reach a certain fraction of the ultimate steady state following first-order input can also be estimated, where the fraction of the steady-state level (f_{ss}) is as defined by Eq. (383), that is, $f_{ss} = \bar{C}_n/\bar{C}$, where $\bar{C}_n = \int_0^\tau C_n\,dt/\tau$ [Eq. (371)] and $\bar{C} = FX_0/VK\tau$ [Eq. (395)]. Integration of (392) from time zero to τ yields

$$\int_0^\tau C_n\,dt = \frac{k_a FX_0}{V(k_a - K)}\left[\left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)\frac{e^{-k_a\tau}}{k_a} - \left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)\frac{e^{-K\tau}}{K} + \left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)\frac{1}{K} - \left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)\frac{1}{k_a}\right] \tag{412}$$

which on rearrangement and simplification becomes

$$\int_0^\tau C_n\,dt = \frac{FX_0}{VK}\left(1 + \frac{Ke^{-nk_a\tau}}{k_a - K} - \frac{k_a e^{-nK\tau}}{k_a - K}\right) \tag{413}$$

Substitution of the value of $\int_0^\tau C_n\,dt$, as given in (413), into (371) yields the following expression for the "average" plasma concentration of drug during the nth dosing interval:

$$\bar{C}_n = \frac{FX_0}{VK\tau}\left(1 + \frac{Ke^{-nk_a\tau}}{k_a - K} - \frac{k_a e^{-nK\tau}}{k_a - K}\right) \tag{414}$$

By substituting $\bar{C}$ for $FX_0/VK\tau$ according to (395) in (414), and dividing both sides of the equation by $\bar{C}$, one obtains

$$f_{ss} = \frac{\bar{C}_n}{\bar{C}} = \left(1 + \frac{Ke^{-nk_a\tau}}{k_a - K} - \frac{k_a e^{-nK\tau}}{k_a - K}\right) \tag{415}$$

From (415) it is readily apparent that the time required to reach a certain fraction of the steady-state level is a complex function of the absorption and elimination rate constants. The larger the value of k_a relative to K, the less dependent on k_a is the time required to reach a given fraction of steady state. At very large values of k_a relative to K (that is, $k_a/K \geq 10$) Eq. (415) approaches

$$f_{ss} = 1 - e^{-nK\tau} \tag{384}$$

Therefore,

$$n\tau = -3.32t_{\frac{1}{2}} \log (1 - f_{ss}) \tag{388}$$

which is readily arrived at from Eq. (385) [4]. Hence, when the absorption rate constant is significantly larger than the elimination rate constant, the time required ($n\tau$) to reach a certain fraction of the steady-state level is a function only of drug elimination [that is, K or $t_{\frac{1}{2}}$, where $t_{\frac{1}{2}} = 0.693/K$, Eq. (12)]. If this is not the case, then f_{ss} is dependent on k_a. The smaller the value of k_a, the longer the time required to attain steady state or some fraction thereof.

As discussed in the section on multiple dosing by intravenous administration, an initial "loading" dose may be desirable, since for drugs with long half-lives a long period of time is required to reach steady state. The "loading" dose X_0^* required to achieve steady-state levels on the first dose may be determined by letting X_0 equal X_0^* in Eq. (406) [the equation for $(C_1)_{min}$] and setting this equal to the equation for $(C_\infty)_{min}$ [Eq. (407)], that is,

$$\frac{k_a FX_0^*}{V(k_a - K)}\left(e^{-K\tau} - e^{-k_a\tau}\right) = \frac{k_a FX_0}{V(k_a - K)}\left(\frac{e^{-K\tau}}{1 - e^{-K\tau}} - \frac{e^{-k_a\tau}}{1 - e^{-k_a\tau}}\right) \tag{416}$$

By cancelling common terms, bringing the right side of the equation to a common denominator, and dividing by $e^{-K\tau} - e^{-k_a\tau}$, one obtains

$$X_0^* = X_0\left[\frac{e^{-K\tau} - e^{-K\tau - k_a\tau} - e^{-k_a\tau} + e^{-K\tau - k_a\tau}}{(1 - e^{-K\tau})(1 - e^{-k_a\tau})(e^{-K\tau} - e^{-k_a\tau})}\right] \tag{417}$$

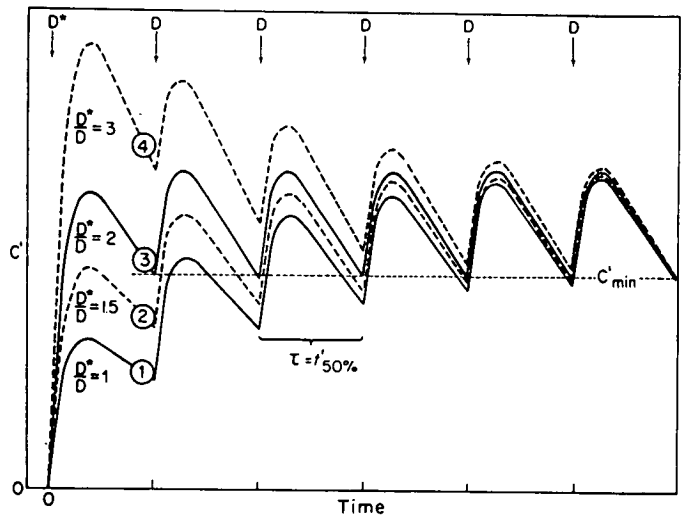

FIG. 3-7. Concentration (c') curves of a drug in the plasma for dosage schedules with equal maintenance doses D and dosing intervals (τ, set equal to the half-life of the drug, $t'_{50\%}$) but different loading doses D^*, such that D^*/D varies from 1 to 3. (From Ref. 5.)

Further simplification gives

$$X_0^* = X_0\left[\frac{1}{(1 - e^{-K\tau})(1 - e^{-k_a\tau})}\right] \tag{418}$$

If the maintenance dose is administered in the postabsorptive phase of the loading dose, (418) can be further simplified since the term $e^{-k_a\tau}$ approaches zero and

$$X_0^* = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) \tag{391}$$

which was the equation employed to calculate a loading dose for drugs administered by the intravenous route. Irrespective of the size of the initial dose the steady-state plasma concentration of drug ultimately reached will be the same since the steady-state level is governed by the size of the maintenance dose (Fig. 3-7).

II. TWO-COMPARTMENT MODEL

A. Intravenous Injection

Plasma levels of a drug which after intravenous administration confers upon the body the characteristics of a two-compartment model can be described by

$$C = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)}e^{-\beta t} \tag{153}$$

where α and β are the fast and slow disposition rate constants, respectively, and k_{21} is an intercompartmental transfer rate constant. V_c is the apparent volume of the central compartment. See Chap. 2 for a more detailed discussion of these parameters. The plasma concentration at any time during a dosing interval can be determined directly by multiplying each exponential term in (153) by the multiple-dosing function (see Appendix 2) and setting k_i in each function equal to the disposition rate constant in each exponential term, that is

$$C_n = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}\left(\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}}\right)e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)}\left(\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}\right)e^{-\beta t} \tag{419}$$

where t is any time during a dosing interval of length τ time units (that is, $0 \leq t \leq \tau$) and n is the number of doses administered. At steady state the terms $e^{-n\alpha\tau}$ and $e^{-n\beta\tau}$ approach zero, and therefore (419) reduces to

$$C_\infty = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}\left(\frac{1}{1 - e^{-\alpha\tau}}\right)e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)}\left(\frac{1}{1 - e^{-\beta\tau}}\right)e^{-\beta t} \tag{420}$$

where C_∞ is the plasma concentration of drug at any time during a dosage interval at steady state following intravenous administration. Equation (420) can also be written in the form

$$C_\infty = Ue^{-\alpha t} + We^{-\beta t} \tag{421}$$

where

$$U = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}\left(\frac{1}{1 - e^{-\alpha\tau}}\right) \tag{422}$$

and

$$W = \frac{X_0(k_{21} - \beta)}{V_C(\alpha - \beta)}\left(\frac{1}{1 - e^{-\beta\tau}}\right) \tag{423}$$

Therefore, from a semilogarithmic plot of plasma concentration versus time during a dosage interval at steady state, U, W, α, and β can be estimated (see method of residuals, Appendix 3). For such estimates to be made, however, τ must be sufficiently large such that administration occurs in the postdistributive phase of the preceding dose. Substitution of A for $X_0(\alpha - k_{21})/V_C(\alpha - \beta)$ and B for $X_0(k_{21} - \beta)/V_C(\alpha - \beta)$, according to (155) and (156), respectively, in (422) and (423) yields

$$U = A\left(\frac{1}{1 - e^{-\alpha\tau}}\right) \tag{424}$$

and

$$W = B\left(\frac{1}{1 - e^{-\beta\tau}}\right) \tag{425}$$

where A and B are the zero-time intercepts following a single intravenous dose. Solving (424) and (425) for A and B, respectively, yields the following expressions:

$$A = U(1 - e^{-\alpha\tau}) \tag{426}$$

and

$$B = W(1 - e^{-\beta\tau}) \tag{427}$$

Therefore, after U, W, α, and β have been determined, A and B can be calculated, and by knowing A, B, α, and β, the parameters for a two-compartment model V_C, k_{21}, k_{10}, k_{12}, and V_B can be calculated employing (163), (165), (166), (167), and (237), respectively.

As discussed in Chap. 2, one frequently finds that the larger the ratio of the zero-time intercepts A/B, the more readily one can discern the two-compartment characteristics of a drug. Following the administration of a single intravenous dose the ratio of A to B is given by

$$\frac{A}{B} = \frac{\alpha - k_{21}}{k_{21} - \beta} \tag{270}$$

However, when a drug is continually administered until attainment of steady state the analogous ratio U/W is

$$\frac{U}{W} = \frac{A(1 - e^{-\beta\tau})}{B(1 - e^{-\alpha\tau})} \tag{428}$$

where U and W are as given by (424) and (425), respectively. Therefore, the ratio U/W will always be less than the ratio A/B since α is by definition greater than β, and hence the ratio $(1 - e^{-\beta\tau})/(1 - e^{-\alpha\tau})$ will always be less than one. Consequently, following multiple dosing the ability to discern the two-compartment characteristics of a drug is usually decreased. For a more detailed discussion of this phenomenon see page 75 in Chap. 2.

The "average" plasma concentration of a drug at steady state $\bar{C}$, as defined by Eq. (365), $\bar{C} = \int_0^\tau C_\infty\, dt/\tau$, can be derived for a drug which upon intravenous administration confers two-compartment model characteristics to the body. The area under the plasma concentration-time curve during a dosing interval at steady state can be obtained by integrating (421) from time zero to τ, that is,

$$\int_0^\tau C_\infty\, dt = \frac{U}{\alpha}(1 - e^{-\alpha\tau}) + \frac{W}{\beta}(1 - e^{-\beta\tau}) \tag{429}$$

Substitution for U and W, according to (424) and (425), respectively, in (429) yields

$$\int_0^\tau C_\infty\, dt = \frac{A}{\alpha} + \frac{B}{\beta} \tag{430}$$

which is equal to the area under the plasma concentration-time curve from time zero to infinity after a single dose, that is,

$$\int_0^\infty C\, dt = \frac{A}{\alpha} + \frac{B}{\beta} \tag{431}$$

The latter is readily obtained by integration of (154) from time zero to infinity. Also, by arranging (232), it can be shown that

$$\int_0^\infty C\, dt = \frac{X_0}{V_C k_{10}} \tag{432}$$

where V_C and k_{10} are the apparent volume of and elimination rate constant from the central compartment, respectively. Therefore,

$$\int_0^\tau C_\infty\, dt = \frac{X_0}{V_C k_{10}} \tag{433}$$

and the "average" plasma concentration of a drug at steady-state $\bar{C}$ is given by

$$\bar{C} = \frac{X_0}{V_c k_{10} \tau} \tag{434}$$

Since $V_c k_{10}$ equals $V_B \beta$ [Eq. (237)], $\bar{C}$ can also be given by

$$\bar{C} = \frac{X_0}{V_B \beta \tau} \tag{435}$$

Therefore, by knowing the apparent volume of distribution and the elimination rate constant of a drug, the "average" plasma concentration at steady state can be predicted for any intravenous dose administered every τ time units. It is also obvious from previous equations that

$$\bar{C} = \frac{\int_0^\infty C \, dt}{\tau} \tag{436}$$

and therefore the "average" plasma concentration of drug at steady state can be calculated from the area under the curve following a single dose.

The minimum concentration of drug in the plasma during a dosage interval $(C_n)_{min}$ can be determined by setting t equal to τ in (419), that is

$$(C_n)_{min} = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)} \left(\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}} \right) e^{-\alpha\tau} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)} \left(\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}} \right) e^{-\beta\tau} \tag{437}$$

Similarly, the minimum plasma concentration at steady state $(C_\infty)_{min}$ is given by

$$(C_\infty)_{min} = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)} \left(\frac{1}{1 - e^{-\alpha\tau}} \right) e^{-\alpha\tau} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)} \left(\frac{1}{1 - e^{-\beta\tau}} \right) e^{-\beta\tau} \tag{438}$$

From these two equations an accumulation factor R can be readily calculated since $R = (C_\infty)_{min}/(C_1)_{min}$ [Eq. (379)]. Therefore, by setting n equal to one in (437),

$$R = \frac{(\alpha - k_{21}) \left(\frac{1}{1 - e^{-\alpha\tau}} \right) e^{-\alpha\tau} + (k_{21} - \beta) \left(\frac{1}{1 - e^{-\beta\tau}} \right) e^{-\beta\tau}}{(\alpha - k_{21}) e^{-\alpha\tau} + (k_{21} - \beta) e^{-\beta\tau}} \tag{439}$$

which is a very complex relationship. However, assuming each dose is administered in the postdistributive phase of the preceding dose, the term $e^{-\alpha\tau}$ will approach zero and (439) reduces to

$$R = \frac{1}{1 - e^{-\beta\tau}} \tag{440}$$

which is identical in form to the equation for R in a one-compartment model [Eq. (376)]. Therefore, if τ is sufficiently long such that each dose is administered in the postdistributive phase of the preceding dose, the extent of accumulation can be predicted simply by knowing the elimination rate constant of a drug, β.

Administration of an initial "loading" dose, X_0^*, would enable the immediate attainment of steady-state plasma levels. This approach would be of particular importance for drugs with long half-lives for which steady-state levels are required for therapeutic effectiveness. The "loading" dose required to immediately reach steady state can be calculated by setting n equal to one and X_0 equal to X_0^* (the required loading dose) in the equation for $(C_n)_{min}$ [Eq. (437)], that is

$$(C_1)_{min} = \frac{X_0^*(\alpha - k_{21})}{V_c(\alpha - \beta)} e^{-\alpha\tau} + \frac{X_0^*(k_{21} - \beta)}{V_c(\alpha - \beta)} e^{-\beta\tau} \tag{441}$$

and then setting $(C_1)_{min}$ equal to $(C_\infty)_{min}$ [Eq. (438)]. Thus,

$$\frac{X_0^*}{V_c(\alpha - \beta)} [(\alpha - k_{21})e^{-\alpha\tau} + (k_{21} - \beta)e^{-\beta\tau}] = \frac{X_0}{V_c(\alpha - \beta)} \left[\left(\frac{\alpha - k_{21}}{1 - e^{-\alpha\tau}} \right) e^{-\alpha\tau} + \left(\frac{k_{21} - \beta}{1 - e^{-\beta\tau}} \right) e^{-\beta\tau} \right] \tag{442}$$

Solving (442) for X_0^* and cancelling common terms yields the following expression:

$$X_0^* = X_0 \left[\frac{\left(\frac{\alpha - k_{21}}{1 - e^{-\alpha\tau}} \right) e^{-\alpha\tau} + \left(\frac{k_{21} - \beta}{1 - e^{-\beta\tau}} \right) e^{-\beta\tau}}{(\alpha - k_{21})e^{-\alpha\tau} + (k_{21} - \beta)e^{-\beta\tau}} \right] \tag{443}$$

If the second dose (i.e., the maintenance dose) is administered in the postdistributive phase of the loading dose, the term $e^{-\alpha\tau}$ approaches zero and (443) can be simplified to yield

$$X_0^* = X_0 \left(\frac{1}{1 - e^{-\beta\tau}} \right) \tag{444}$$

Therefore, once the maintenance dose X_0 and dosing interval have been determined to produce the desired steady-state plasma levels of drug, the "loading" dose X_0^* can be readily estimated from (444).

B. First-order Absorption

First-order absorption of drugs which confer two-compartment characteristics to the body, yield plasma levels as a function of time which are described by equation (279). Upon multiple dosing the plasma levels of drug during any dosing interval n are given by

$$C_n = \frac{k_a F X_0}{V_c}\left[\frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)}\left(\frac{1-e^{-n\alpha\tau}}{1-e^{-\alpha\tau}}\right)e^{-\alpha t} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)}\left(\frac{1-e^{-n\beta\tau}}{1-e^{-\beta\tau}}\right)e^{-\beta t} + \frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)}\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_a t}\right] \quad (445)$$

where $0 \le t \le \tau$. Equation (445) is obtained by multiplying each exponential term in (279) by the multiple-dosing function (see Appendix 2) and setting k_i in each function equal to the rate constant in each exponential term. Equation (445) can also be written

$$C_n = L\left(\frac{1-e^{-n\alpha\tau}}{1-e^{-\alpha\tau}}\right)e^{-\alpha t} + M\left(\frac{1-e^{-n\beta\tau}}{1-e^{-\beta\tau}}\right)e^{-\beta t} + N\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_a t} \quad (446)$$

where L, M, and N are as defined by (282), (283), and (284), respectively.

Once steady state is attained (i.e., the terms $e^{-n\alpha\tau}$, $e^{-n\beta\tau}$, and $e^{-nk_a\tau}$ approach zero), (446) becomes

$$C_\infty = L\left(\frac{1}{1-e^{-\alpha\tau}}\right)e^{-\alpha t} + M\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta t} + N\left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a t} \quad (447)$$

where C_∞ is the plasma concentration of drug during a dosing interval at steady state. Integration of (447) from time zero to τ yields the area under the plasma concentration versus time curve at steady state, that is,

$$\int_0^\tau C_\infty\, dt = \frac{L}{\alpha} + \frac{M}{\beta} + \frac{N}{k_a} \quad (448)$$

which is equal to $\int_0^\infty C\, dt$ following a single dose [Eq. (285)]. The area under the curve after a single dose is also given by

$$\int_0^\infty C\, dt = \frac{FX_0}{V_c k_{10}} \quad (290)$$

and therefore

$$\int_0^\tau C_\infty\, dt = \frac{FX_0}{V_c k_{10}} \quad (449)$$

where k_{10} is the elimination rate constant from the central compartment. Since $\bar{C}$ is equal to $\int_0^\tau C_\infty\, dt/\tau$ [Eq. (365)],

$$\bar{C} = \frac{FX_0}{V_c k_{10}\tau} \quad (450)$$

Furthermore, $V_c k_{10}$ equals $V_B\beta$ [Eq. (237)], and therefore $\bar{C}$ is also given as follows:

$$\bar{C} = \frac{FX_0}{V_B\beta\tau} \quad (451)$$

It follows that the "average" plasma concentration of a drug at steady state is independent of α and the absorption rate constant, and can be predicted employing (451) provided the fraction of dose absorbed, the apparent volume of distribution, and the elimination rate constant of a drug are known.

A more useful approach, which would not require estimates of F, V_B, and β, is based on the equality $\int_0^\tau C_\infty\, dt = \int_0^\infty C\, dt$ and is given as $\bar{C} = \int_0^\infty C\, dt/\tau$ [Eq. (436)]. This equation can be employed regardless of the route of administration (provided F is independent of dose number), and for any N compartment mammillary model provided elimination occurs exclusively from the central compartment. The utility of this approach for predicting $\bar{C}$ is illustrated by Fig. 3-8.

As has been discussed previously, the extent to which a drug will accumulate following multiple dosing can be determined by comparing the minimum plasma concentrations of drug at steady state with that after the first dose [i.e., the accumulation factor R equals $(C_\infty)_{min}/(C_1)_{min}$, Eq. (379)]. The equations for the minimum plasma concentrations following the first dose and any dose in the steady state can be obtained by setting t equal to τ in (446) and (447), and setting n equal to one in (446). Therefore,

$$(C_1)_{min} = Le^{-\alpha\tau} + Me^{-\beta\tau} + Ne^{-k_a\tau} \quad (452)$$

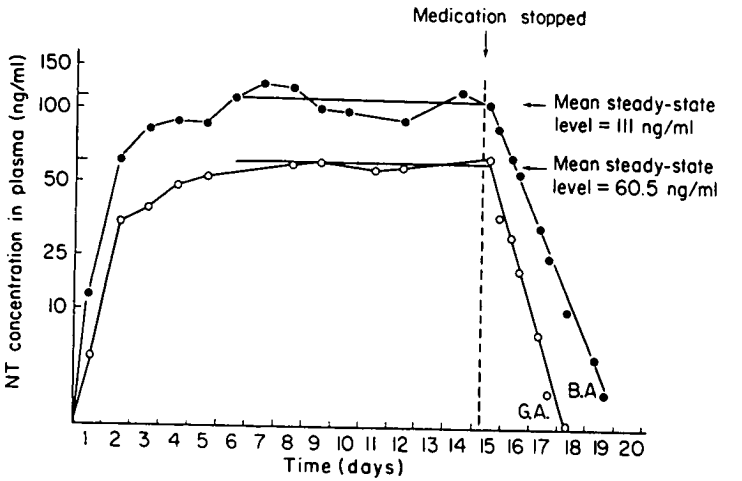

FIG. 3-8. Semilogarithmic plot of nortriptyline (NT) concentration in the plasma versus time after multiple doses (0.4 mg/kg, three times a day) to two normal subjects, G.A. (o) and B.A. (•). Mean steady-state levels predicted after single-dose administration of NT to these subjects are 53 ng/ml and 116 ng/ml for G.A. and B.A., respectively. (From Ref. 6.)

and

$$(C_\infty)_{min} = L\left(\frac{1}{1-e^{-\alpha\tau}}\right)e^{-\alpha\tau} + M\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta\tau} + N\left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a\tau} \tag{453}$$

Hence

$$R = \frac{L\left(\frac{1}{1-e^{-\alpha\tau}}\right)e^{-\alpha\tau} + M\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta\tau} + N\left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a\tau}}{Le^{-\alpha\tau} + Me^{-\beta\tau} + Ne^{-k_a\tau}} \tag{454}$$

However, if τ is of sufficient length such that the drug is administered in the postabsorptive, postdistributive phase of the preceding dose, then (454) simplifies to

$$R = \frac{1}{1-e^{-\beta\tau}} \tag{440}$$

This equation readily permits the estimation of the extent to which a drug accumulates in the body following first-order input. Only an estimate of the elimination rate constant is required.

The same approach for calculating a "loading" dose as used in Sec. II.A can be used for drugs administered by first-order input (i.e., by administering an initial "loading" dose X_0^* of sufficient magnitude such that $(C_1)_{min} = (C_\infty)_{min}$). The analogous expression to Eq. (443) would then be

$$X_0^* = X_0\left[\frac{\frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)}\frac{e^{-\alpha\tau}}{1-e^{-\alpha\tau}} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)}\frac{e^{-\beta\tau}}{1-e^{-\beta\tau}} + \frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)}\frac{e^{-k_a\tau}}{1-e^{-k_a\tau}}}{\frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha\tau} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)}e^{-\beta\tau} + \frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)}e^{-k_a\tau}}\right] \tag{455}$$

However, by administration of the maintenance dose in the postabsorptive, postdistributive phase of the "loading" dose the following equation is obtained:

$$X_0^* = X_0\frac{1}{1-e^{-\beta\tau}} \tag{444}$$

from which it is relatively simple to estimate a "loading" dose.

REFERENCES

1. Krüger-Thiemer, E., Berlin, H., Brante, G., Bunger, P., Dettli, L., Spring, P., and Wempe, E.: Dosage regimen calculations of chemotherapeutic agents V. 2-Sulfanilamido-3-methoxy-pyrazine (sulfalene), Chemother., 14: 273 (1969).

2. Buchanan, R. A., Kinkel, A. W., Goulet, J. R., and Smith, T. C.: The metabolism of diphenylhydantoin (dilantin) following once-daily administration, Neurol., 22: 1809 (1972).

3. Platt, D. S.: Plasma concentrations of griseofulvin in human volunteers, Br. J. Derm., 83: 382 (1970).

4. Van Rossum, J. M., and Tomey, A. H. M.: Rate of accumulation and plateau plasma concentration of drugs after chronic medication, J. Pharm. Pharmacol., 20: 390 (1968).

5. Krüger-Thiemer, E., and Bunger, P.: The role of the therapeutic regimen in dosage design I., Chemother., 10: 61 (1965/66).

6. Alexanderson, B.: Pharmacokinetics of nortriptyline in man after single and multiple oral doses: The predictability of steady-state plasma concentrations from single dose plasma-level data, Eur. J. Clin. Pharmacol., 4: 82 (1972).

Chapter 4

BIOAVAILABILITY

Bioavailability has been defined as the measurement of both the relative amount of an administered dose that reaches the general circulation (i.e., the extent of absorption of a given dose) and the rate at which this occurs [1]. For drugs that are administered on a continuous basis (i.e., in a "chronic" fashion), the total amount of drug absorbed is usually much more critical than its rate of absorption. This point has been amply demonstrated in the previous chapter. However, the absorption rate (rather than the extent of absorption) may be the more critical pharmacokinetic parameter in the totality of drug effect of those substances that may be used effectively as a single dose. A drug that enters the circulation very rapidly might induce, initially, untoward reactions if the body burden is excessive. On the other hand, if the drug is absorbed too slowly, it may not achieve sufficient body levels to produce a desired effect or a desired intensity of pharmacologic response, even if the entire dose is ultimately absorbed. It is equally obvious that the onset of pharmacologic response from a single dose of a drug is directly influenced by the rate of availability. Also, in our view, it is fair to state that the significant present-day interest in absorption kinetics has been stimulated by pharmaceutical scientists in their quest for in vitro methodology which will provide data to mirror dosage form performance with respect to drug release in and absorption from the gastrointestinal tract. We must state at the outset that assessments of the rate of availability is one of the most difficult problems encountered in developing a pharmacokinetic profile of a drug since these assessments are always model-dependent and must frequently be attempted with the most shocking paucity of data.